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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/776,504      | 02/12/2004  | Ralph M. Ellison     | 077319-0399         | 3667             |

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EXAMINER

PAK, JOHN D

ART UNIT PAPER NUMBER

1616

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE  | DELIVERY MODE |
|--|------------|---------------|
| 3 MONTHS                               | 01/24/2007 | PAPER         |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

**Office Action Summary**

Application No.

10/776,504

Applicant(s)

ELLISON ET AL.

Examiner

JOHN PAK

Art Unit

1616

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 November 2006.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,3-12,19-22 and 24 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-12,19-22 and 24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

Claims 1, 3-12, 19-22 and 24 are pending in this application. Independent claim 1 has been amended so that it now recites a method of treating specific subtypes of acute myelogenous leukemia: acute myeloblastic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia or acute erythroleukemia. Such claim feature has not been examined before. The following new grounds of rejection are set forth.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3-12, 19-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shen et al. in view of Chen et al., Kwong et al., Saito et al. and Medline abstract 82120536.

Shen et al. disclose intravenously administering 10 mg arsenic trioxide in glucose and saline to patients who have APL, acute promyelocytic leukemia (which is a type of acute myelogenous leukemia, AML). See the entire article, in particular page 3354, right column, last paragraph. All patients were previously treated with all-trans retinoic acid, ATRA (page 3358, right column, lines 8-11). Two patients were treated with ATRA during the remission induction period (page 3358, right column, lines 21-31; see also page 3356, left column, lines 8-9). Shen's patients who received both arsenic trioxide

and ATRA did not respond to ATRA alone (page 3358, right column, lines 23-25). Other patients received danorubicin + cytosine arabinoside, harringtonine or hydroxyurea in addition to arsenic trioxide (Table 2 on page 3355).

Chen et al.<sup>1</sup> disclose arsenic trioxide to be effective and relatively safe in the treatment of APL (abstract, pages 3351-52). Arsenic trioxide as a dose-dependent dual effect on APL cells, wherein apoptosis occurs at higher concentrations and differentiation occurs at lower concentrations (page 3351, left column, last full paragraph). Partial differentiation of APL cells followed by cell death is also disclosed (id.). Lack of cross-resistance is disclosed between arsenic trioxide and all-trans retinoid acid (page 3345, left column, second paragraph).

Kwong et al.<sup>2</sup> disclose the use of arsenic trioxide for treating chronic myeloid leukemia (CML) and acute myeloid leukemia (AML). See page 3487. 10 mg/day of arsenic trioxide via IV resulted in complete morphologic remission in acute promyelocytic leukemia (APL) patients (left column of page 3487, first paragraph). Arsenic trioxide is disclosed as "effective for leukemias of different morphologic types" and such activity is disclosed to be related to intrinsic toxicity of arsenic to marrow cells (page 3487, right column). Arsenic trioxide is also disclosed to induce apoptosis and differentiation of APL cells (page 3487, right column, last sentence).

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<sup>1</sup> Chen et al., Blood, Vol. 89(9), pages 3345-53, cited by applicant in the IDS of 5/19/04.

<sup>2</sup> Kwong et al., Blood, Vol. 89, pages 3487-88 (May 1997), cited by applicant in the IDS of 5/19/04.

Saito et al.<sup>3</sup> disclose that ATRA is known to induce complete remission of APL (page 657, first paragraph after abstract). ATRA provides rapid amelioration of disseminated intravascular coagulation syndrome, DIC, which can arise from **APL and acute monoblastic leukemia**<sup>4</sup> (page 657, abstract and first two paragraphs). ATRA has **the same effect** of upregulating thrombomodulin (TM) and downregulating tissue factor (TF) expression in **APL cells and acute monoblastic leukemia cells (U937)**, which upregulation and downregulation are “major factors in the improvement of DIC.” See abstract; first page 657, first paragraph; page 663, right column, first full paragraph. Retinoic acids, including ATRA, have anticoagulant effect, which is inducible not only to **M3 and M5 subtypes** (i.e. **APL and acute monoblastic leukemia, respectively**) of established cell lines but also to M3, M5 and a part of the **other types of AML of leukemic cells freshly isolated** from patients (page 662, right column, second paragraph).

Medline abstract 82120536 discloses that retinoic acid, including ATRA, inhibits the clonal growth and proliferation of **acute myeloblastic leukemia and APL** human cell lines.

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<sup>3</sup> Saito, T. et al., Blood, Vol. 87(2), pages 657-665 (1/1996).

<sup>4</sup> Acute monoblastic leukemia is the same as acute monocytic leukemia.

The difference between the claimed invention and the cited references is that the references do not explicitly disclose treatment of specific subtypes of acute myelogenous leukemia, i.e. acute myeloblastic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia or acute erythroleukemia, by administering a combination of arsenic trioxide and ATRA. However, **arsenic trioxide + ATRA** is a known combination for treatment of APL, and both arsenic trioxide and ATRA are taught to provide efficacy against **many different types of leukemia**. Shen et al., Chen et al. and Kwong et al. combine to establish that **arsenic trioxide is known to be effective against APL, AML and CML**. Kwong et al. disclose, "As<sub>2</sub>O<sub>3</sub> appeared to be effective for leukemias of different morphologic types" (page 3487, right column). Additionally, **ATRA has been taught to be effective against APL, acute monoblastic (monocytic) leukemia and acute myeloblastic leukemia** (Saito et al. and Medline abstract 82120536). Thus, one having ordinary skill in the art would have been motivated to administer arsenic trioxide + ATRA to at least treat acute monocytic leukemia and acute myeloblastic leukemia and would have had reasonable expectation of success.

The cited references do not explicitly disclose a further combination of at least one more therapeutic agent as set forth in applicant's claims 9-11. However, such combination therapies would have been fairly suggested from the conventional practice in the cancer treatment field to combine the actions and benefits of several therapies to

attack the cancer cells from a variety of mechanisms. A substance such as cisplatin is a well known anticancer agent and its use in combination with arsenic trioxide and ATRA would have been obvious from the motivation to control the cancer cells via various approaches.

Applicant's claim 12 recites dosing based on body weight. Such dose adjustment would have been obvious from the motivation to tailor the amount of the arsenic trioxide to obtain the maximum therapeutic benefit while keeping side effects to tolerable levels. Smaller individuals who weigh less are less likely to tolerate higher amounts, so it would have been obvious to vary the dose according to body weight.

Motivation to treat metastasized cancer would have been found from the efficacy of these combination treatments against various anti-cancer mechanisms.

Timing of ATRA treatment would have been within the skill of the ordinary skilled artisan, who would have been motivated to use the treatment before, after or concurrently with arsenic trioxide depending on patient condition and the severity of leukemia.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

Applicant will no doubt recognize that this is a new ground of rejection with new prior art references to address applicant's amendatory subject matter. Applicant argued in the remarks filed on 11/1/2006 that those skilled in the art would not have reasonably expected that a combination of arsenic trioxide and ATRA could have been successfully used to treat non-APL AML subtypes in humans just because the combination had been reported to have efficacy against APL. However, applicant's argument, based on the claims as currently amended, is sufficiently countered by the new combination of prior art references. Arsenic trioxide is known to be effective against many different types of leukemia, including APL, AML and CML (Shen et al., Chen et al., Kwong et al.). Kwong et al. disclose, "As<sub>2</sub>O<sub>3</sub> appeared to be effective for leukemias of different morphologic types" (page 3487, right column). Additionally, **ATRA has been taught to be effective against APL, acute monoblastic (monocytic) leukemia and acute myeloblastic leukemia** (Saito et al. and Medline abstract 82120536). Thus, one having ordinary skill in the art would have been motivated to administer arsenic trioxide + ATRA to at least treat acute monocytic leukemia and acute myeloblastic leukemia and would have had reasonable expectation of success.

Claims 1, 3-12, 19-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shen et al. in view of Chen et al., Kwong et al., Saito et al., Medline abstract 82120536 and Witte et al. (US 4,599,305).



Teachings of all references except for Witte et al. were discussed above, and the discussion there is incorporated herein by reference.

Witte et al. establish that various treatments are known for leukemia treatment, wherein acute leukemia “requires immediate treatment utilizing the full range of therapeutic measures available,” such as radiation therapy and chemotherapy (column 1, lines 32-45). Radiation is used to treat both chronic lymphoid leukemia and acute leukemias (id.).

The Examiner incorporates herein by reference the full rationale set forth in the immediately preceding ground of rejection. Witte et al. add to the understanding of the level of the skill of the ordinary skilled person in this art by further making clear that combination of multiple treatment agents for leukemia would have been fairly suggested from the conventional practice in the leukemia treatment field to combine the actions and benefits of several therapies to attack the cancer cells from a variety of mechanisms.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620**. The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Johann Richter, can be reached on **(571)272-0646**.

The fax phone number for the organization where this application or proceeding is assigned is **(571)273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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